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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/528,978	Applicant(s) OBACH, R. SCOTT	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2003 and 18 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on February 14, 2003 in Paper No. 10 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/528,978 is acceptable and a CPA has been established. An action on the CPA follows.

This Office Action is a response to Applicant's CPA filed February 14, 2003 in Paper No. 10, and amendment and response to the Office Action (mailed August 14, 2001), filed on March 18, 2002 in Paper No. 7 wherein claims 2-5, 7-10, 12-13, and 14-22 are cancelled and claim 1 has been amended. It is noted that no response and/or amendment in response to the Final Office Action (June 5, 2002) is filed.

Applicant's preliminary amendment in Paper No. 11, submitted May 8, 2003, is acknowledged, wherein the instant specification has been amended as to the first line to claim the priority to the provisional application herein.

Currently, claims 1, 6, and 11 are pending in this application.

Claims 1, 6, and 11 are examined on the merits herein.

It is noted that Applicant's election with traverse of the elected species of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine in claim 6 and quindine in claim 11 in Paper No. 4, submitted July 26, 2001. See the Office Action (mailed August 14, 2001).

Claim R jections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular CYP2D6 substrates or drug for CYP2D6 mediated oxidative biotransformation disclosed in the specification (see page 4), and co-administering the particular CYP2D6 inhibitors disclosed in the specification (see page 4) in claimed method herein, does not reasonably provide enablement for the employment any CYP2D6 substrates in combination with any CYP2D6 inhibitors in the claimed methods of the particular treatments herein.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of administering a combination herein for therapy.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claim 1 is deemed very broad since the claim reads on any CYP2D6 substrates in combination with any CYP2D6 inhibitors employed in the claimed method herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, a CYP2D6 substrate in combination with a CYP2D6 inhibitor recited in the instant claim are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds for each kind of functional

compounds for the claimed method of administering herein (see page 3 of the specification).

Thus, Applicants functional language at the points of novelty in claims 1-2 fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph.

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for the combination herein, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) the *combination* of any compounds represented

by CYP2D6 substrates and CYP2D6 inhibitors, and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant

claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benet et al. (5,567,592) and Hess (WO 96/14845) for reasons of record stated in the previous Office Actions dated August 14, 2001 and June 5, 2002.

Benet et al. teaches the administration a drug that is the particular cytochromes P450, CYP2D6 substrate which is a member of CYP family, in mediating oxidative biotransformation for the major clearance mechanism in humans. See col.1-2. Benet et al. also teaches that CYP2D6 inhibitors such as quinidine, calcium channel blockers, and phenothiazines are useful as bioenhancers to increase the bioavailability of a pharmaceutical compound through the inhibition of cytochrome P450. See col.2 lines 46 – col.3 lines 25, and col.7. Benet et al. further teaches that a drug having activity of CYP3A (CYP3A substrate), another particular member of CYP family in combination with a CYP3A inhibitor which is not the same compound in the instant method for the improvement of drug bioavailability and major clearance. See col.9-11 Table 1.

Hess discloses that the instant elected species, (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, is a NK-1 receptor antagonist containing a secondary alkylamine. See abstract, page 22, lines 24-25, and page 152 lines 33-34 (claim 10):

The prior art does not expressly disclose the employment of (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine as a CYP2D6 substrate in mediating oxidative biotransformation in combination with quinidine as a CYP2D6 inhibitor to be administered in a method for the major clearance mechanism in humans.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine as CYP2D6 in mediating oxidative biotransformation in combination with quinidine as a CYP2D6 inhibitor to be administered in a method for the major clearance mechanism in humans.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine as a CYP2D6 substrate in mediating oxidative biotransformation in combination with quinidine as a CYP2D6 inhibitor to be administered in a method for the major clearance mechanism in humans since NK-1 receptor antagonists are well known CYP2D6 substrates. It is well known that CYP2D6 substrates mediate oxidative biotransformation for the major clearance mechanism in humans. Moreover, quinidine is well known to be a CYP2D6 inhibitor, useful in a method for enhancing drug pharmacokinetic profile and the major clearance mechanism. Further, it is known that the employment of a drug having CYP3A activity within the same CYP family (a CYP3A substrate) in combination with a CYP3A inhibitor which is not the same compound is useful in the same method for improvement of the improvement of drug bioavailability and major clearance according to Benet et al. Therefore, one of ordinary skill in the art would have reasonably expected that combining (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, a CYP2D6 substrate, in combination with quinidine, a CYP2D6 inhibitor, known useful for the same purpose in a composition to be administered would be useful

for the instant claimed method as same as the combination of a CYP3A substrate and a CYP3A inhibitor does.

Applicant's remarks filed on March 18, 2002 in Paper No. 7 with respect to this rejection of claims 1, 4, 6, and 11 made under 35 U.S.C. 103(a) of record stated in the previous Office Action (August 14, 2001) have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art for the following reasons.

Applicant's assertion that the there is no motivation or suggestion whatsoever in the prior art to use the claimed combinations has been considered but is not found persuasive. It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06. In the instant case, as discussed in the previous Office Action, both NK-1 receptor antagonists including the elected species, (2S,3S)-2-phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine, and quinidine are well known CYP2D6 substrates, as taught by Applicant's admission regarding the prior art in the instant specification (see page 4 lines 5-8 and 14-26). Moreover, as discussed in the previous Office Action, it is well known that CYP2D6 substrates mediate oxidative biotransformation for the major clearance mechanism in humans. Therefore, one of ordinary skill in the art would have reasonably

expected that combining two particular CYP2D6 substrates (two instant elected species) known useful for the same purpose, i.e., mediating oxidative biotransformation for the major clearance mechanism in humans, in a composition to be administered would produce additive therapeutic effects to improve the same treatment, absent evidence to the contrary.

Since all active composition components herein are known to useful to be CYP2D6 substrates, mediating oxidative biotransformation for the major clearance mechanism in humans, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected based on the well settled principle set forth *In re Kerkhoven* regarding combination inventions.

Additionally, Applicant arguments that the examiner has made parallels with other enzyme, CYP3A, with CYP2D6, according to Benet's teaching regarding the combination of two CYP3A, have been considered but not found persuasive. Benet's teaching regarding the combination of two CYP3A have been cited by the examiner primarily for this teaching further provides motivation to employ the combination herein.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

The record contains no clear and convincing evidence of nonobviousness or unexpected results for the combination herein over the prior art. In this regard, it is

noted that the specification provides no side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
June 17, 2003